P20428.A07

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Y. AIDA et al.

Art Unit: 1645

Appl. No. : 09/748,131

Examiner: C. J. Marla

Filed : December 27, 2000

For : A METHOD FOR TYPING POLYMORPHISMS OF BOVINE MHC CLASS II GENES

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CD
4/17/02

AMENDMENT UNDER 37 C.F.R. § 1.111

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Responsive to the Office Action of November 30, 2001, reconsideration and withdrawal of the rejections made therein are respectfully requested, in view of the following amendments and remarks. Inasmuch as the three-month shortened statutory period was originally set in the Office Action to expire on February 28, 2002, Applicants hereby request an extension of time for one (1) month and are concurrently filing a formal Request for Extension of Time, together with all requisite fees therefor. If for any reason the formal Request for Extension of Time is not associated with the file at the Patent and Trademark Office or the extension fee is deficient, this should be considered to be an express request for any necessary extension of time and authorization for the Commissioner to charge any necessary extension of time fee to Deposit Account No. 19-0089.

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IN THE SPECIFICATION

Please amend the specification as follows (*a marked up copy of the Specification amendments is provided as an attachment to this Response*):

Page 8, please replace the first paragraph of Example 1 with the following,

20 to 40μg of genomic DNA prepared from a bovine individual by simple extraction method was dissolved in 50μl×1 rTaq buffer (10mM Tris-HCl, 50mM KCl, 0.1% TritonX-100) containing 120μl of each dNTP, 1.5mM MgCl2, 0.2μm of each primer and 2 units of recombinant Ta1 DNA elongation enzyme (rTaq)(TOYOBO). The solution was heated at 95°C for 5 minutes for denaturation, and then a cycle of reactions at 95°C for 50 seconds for denaturation, at 60°C for 50 seconds for annealing, and at 72°C for 50 seconds for elongation was repeated for 20 cycles. Then, elongation at 72°C for 2 minutes was performed. Primers used were those capable of specifically amplifying DRB3 gene exon 2 by PCR which encodes ß1 domain of bovine MHC Class II DRßchain (BoLA-DRß).

B1

ERB3 : 5'- GGA ATT CCT CTC TCT GCA GCA CAT TTC C -3'

(The nucleotide sequence of ERB3 is shown as SEQ ID NO:10.)

HL031 : 5'- TTT AAA TTC GCG CTC ACC TCG CCG CT -3'

(The nucleotide sequence of HLO31 is shown as SEQ ID NO:11.)

Pages 8-9, please replace paragraphs (a), (b) and (B) of Example 1 with the following

(a) Forward primers specific for respective allele groups:

B2

sp1: 5'- TGT AAA ACG ACG GCC AGT AGC ACA TTT CCT GCA GTA TC -3'

sp2: 5'- TGT AAA ACG ACG GCC AGT AGC ACA TTT CCT GGA GTA TTC TAA -3'

sp3: 5'- TGT AAA ACG ACG GCC AGT AGC ACA TTT CCT GGA GTA TTA -3'

sp4: 5'- TGT AAA ACG ACG GCC AGT AGC ACA TTT CCT GGA GTA TTG -3'

sp5: 5'- TGT AAA ACG ACG GCC AGT CAC ATT TCC TGG AGT AGT -3'

sp6: 5'- TGT AAA ACG ACG GCC AGT GCA CAT TTC CTG GAG TAT C -3'

sp7: 5'- TGT AAA ACG ACG GCC AGT AGC ACA TTT CCT GGA GTA TA -3'

sp8: 5'- TGT AAA ACG ACG GCC AGT CAC ATT TCC TGG AGT ATT CTA C -3'

B2 (Nucleotide sequences of sp1 to sp8 are shown as SEQ ID NOS: 1 to 8, respectively.)

(b) Reverse primer:

The following primer was designed as a primer capable of amplifying all alleles.

DRB3B: 5'- CAG GAA ACA GCT ATG ACC CGC CGC TGC ACA GTG AAA CTC -3'

(The nucleotide sequence of DRB3B is shown as SEQ ID NO:9.)

(B) PCR capable of amplifying all alleles:

25μl×1 GeneAmpR Gold Buffer (PE Biosystems), containing 120μl of each dNTP, 1.5mM MgCl2, forward primer capable of amplifying 0.2μM of all allele groups, 0.2μl of reverse primer, 1 unit of AmpliTaq GoldTM DNA elongation enzyme and 1μl of the above obtained PCR products, was heated at 95°C for 10 minutes for denaturation as a pretreatment, and then a cycle of reactions at 95°C for 1minute for denaturation, at 64°C for 30 seconds for annealing, and at 72°C for 30

seconds for elongation was repeated for 20 cycles. Then, elongation at 72°C for 5 minutes was performed.

(a) Forward primer:

DRB3ALL: 5'- TGT AAA ACG ACG GCC AGT ATT CCT CTC TCT GCA GCA CAT TTC CTG -3'

B2

(The nucleotide sequence of DRB3BALL is shown as SEQ ID NO:12.)

(b) Reverse primer:

DRB3B: 5'- CAG GAA ACA GCT ATG ACC CGC CGC TGC ACA GTG AAA CTC -3'

(The nucleotide sequence of DRB3B is shown as SEQ ID NO:9.)

IN THE CLAIMS

Please cancel claims 7-13 without prejudice or disclaimer of the subject matter recited therein.

Please amend claims 1-6, and 14-15 as follows (*a marked up copy of the Specification amendments is included in an Appendix attached to this Response*):

1. (Amended) A method for amplifying DNA molecules encoding BoLA-DRB3.2 for typing alleles which comprises performing PCR with a reverse primer which amplifies all alleles of BoLA-DRB3.2, and a forward primer which amplifies all alleles in any one of two or more groups of alleles of BoLA-DRB3.2 wherein each of said groups comprises at least one allele, but which cannot amplify any allele(s) in the other group(s).

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2. (Amended) The method according to claim 1 wherein the forward primer comprises a portion of a DNA sequence encoding an amino acid sequence of the first hypervariable region of BoLA-DRB3.2.

3. (Amended) The method according to claim 1 wherein 96 kinds of alleles of BoLA-DRB3.2 are classified into the two or more groups of alleles of BoLA-DRB3.2.

4. (Amended) The method according to claim 1 wherein 96 kinds of alleles of BoLA-DRB3.2 are classified into 8 groups, and wherein the forward primer set amplifies all alleles in any one of said 8 groups but which cannot amplify any alleles in the other groups.

5. (Amended) The method according to claim 1 wherein the forward primer comprises any one of the sequences of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7 and 8.

6. (Amended) The method according to claim 1 wherein the reverse primer comprises the sequence of SEQ ID NO: 9.

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14. (Amended) A method for typing polymorphisms of DNA encoding BoLA-DRB3.2, which comprises:

(1) performing PCR using a bovine genomic DNA or a DNA fragment thereof as a template, a reverse primer which amplifies all alleles of BoLA-DRB3.2, and a forward primer which amplifies all alleles in any one of two or more groups of alleles of BoLA-DRB3.2 wherein each of said group comprises at least one allele, but is incapable of amplifying any allele(s) in the other group(s); and

(2) where at least two PCR products are amplified in (1), directly sequencing each of the amplified products, and where one PCR product is amplified in (1),sequencing of the amplified product by using a primer set which amplifies all alleles of BoLA-DRB3.2; and

(3) comparing resulting sequence(s) with known sequences of alleles and typing the polymorphisms.

B4

15. (Amended) The method according to claim 14, wherein PCR is performed by using a primer set which amplifies all alleles of BoLA-DRB3.2 using a bovine genomic DNA as a template, and then (1) is performed by using a resulting amplified product as a template.

Please add claims 16-20 as follows:

16. The method according to claim 14 wherein the forward primer comprises a portion of a DNA sequence encoding an amino acid sequence of the first hypervariable region of BoLA-DRB3.2.

17. The method according to claim 14 wherein 96 kinds of alleles of BoLA-DRB3.2 are classified into the two or more groups of alleles of BoLA-DRB3.2.

B5

18. The method according to claim 14 wherein 96 kinds of alleles of BoLA-DRB3.2 are classified into 8 groups, and wherein the forward primer set amplifies all alleles in any one of said 8 groups but which cannot amplify any alleles in the other groups.

19. The method according to claim 14 wherein the forward primer comprises any one of the sequences of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7 and 8.

20. The method according to claim 14 wherein the reverse primer comprises the sequence of SEQ ID NO: 9.

REMARKS

Initially, Applicants thank the Examiner for returning duly initialed copies of the Forms PTO-1449 with the Office Action, indicating consideration of the disclosure statements filed March 26, 2001, June 5, 2001, and June 18, 2001.

Applicants also thank the Examiner for acknowledgment of the claim of priority, and the receipt of certified copies of the priority document.

Reconsideration and withdrawal of the rejections of record are respectfully requested.

Summary of Status of Amendments and Office Action

In the present amendment, claims 1-6 and 14-15 are amended, claims 7-13 are canceled and new claims 16-20 are added. Therefore, claims 1-6 and 14-20 are pending in the application with claims 1 and 14 being independent.

In the Office Action, the specification is objected to objected to for failure to comply with the requirements of 37 C.F.R. §1.821(d).

Claims 1-4, 7-10, 14 and 15 are rejected under 35 U.S.C. § 112, first paragraph, as not described in sufficient detail to reasonably convey to one of skill in the art that the inventor had possession of the claimed invention.

Claims 4, 5, 10, 11, 14 and 15 are objected to under 37 C.F.R. 1.75(c) as being improper because multiple dependent claims cannot themselves depend from a multiply dependent claim.

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 1-4, 7-10 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ellergren et al. (Animal Genetics (1993) 24:269-275).

Claims 7- 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sitte (Animal Genetics (1996) 27:271-273).

Claims 1-4 and 6-10 are rejected under 35 U.S.C. § 102() [the Office Action did not specify which section of 102 was used as the basis for the rejection] being anticipated by Aida (U.S. Patent No. 6,284,457).

Explanation and Support for Amendments

Applicants submit that each of the foregoing amendments is fully supported by the specification, *e.g.* pages 5-7. Further, many of the amendments are in accordance with the Examiner's suggestions in the Office Action.

Response to Objections

Applicants note that the current amendments to the specification identify each sequence by the corresponding SEQ ID NO:. Thus, it is respectfully requested that the Examiner withdraw the objection to the specification.

Applicants note that the current amendments to claims 4, 5 and 14 have eliminated the multiple dependence of the claims. Thus, it is respectfully requested that the Examiner withdraw the objection to claims 4, 5, 14 and 15.

Response to §112, First Paragraph Rejection

Applicants respectfully traverse the rejection of claims 1-4, 7-10, 14 and 15 under 35 U.S.C. § 115, first paragraph. The rejection asserts that the specification has not adequately described the broadly claimed genus of probes which are defined only in terms of their functional activity and are not defined with respect to their structural properties.

In response, Applicants note that *Vas-Cath* and *Eli Lilly* make clear that the specification must convey to one of skill in the art that he/she was in possession of the claimed invention at the time of filing. Applicants also note that *Vas-Cath* and *Eli Lilly* clearly state that question regarding the sufficiency of the written description is factual and depends on the nature of the invention and the knowledge imputed to those skilled in the art.

Applicants respectfully submit that with regard to the primers, the recitation of 8 forward and one reverse primer is representative of the genus' claimed. Applicants submit that one of skill in the art understands that an "allele-specific primer" (the forward primer) anneals to one and only one allele of a gene, and a "non-allele specific primer" (the reverse primer) means a primer which anneals to a all alleles of a gene. Given a gene of known sequence, one of skill in the art can make a primer which is non-allele specific, especially in a situation such as here, where the regions of high and low polymorhisms are known. Further, once regions of high polymorphism have been identified, one of skill in the art can make an allele-specific primer. Thus, Applicants recitation of one non-allele specific primer and 8 allele-specific primers is representative of the claimed genus' for primers, as one of skill in the art, having the published sequence of BoLA-DRB3.2, would know how to create non-allele specific and allele-specific primers. Applicants respectfully submit that

one of skill in the art would understand that Applicants could make any such primer and had such in their possession at the time of filing.

Applicants remind the Examiner that the burden of proving an inadequate written description is on the Examiner, who must give technical reasons for the rejection, and may not simply assert the inadequacy of the disclosure.

Applicants respectfully request that the Examiner withdraw the rejection of claims 1-6 and 14-15 under §112, first paragraph.

Response to §112, Second Paragraph Rejections

Applicants note that the amendments to claims 1-6 and 14-15 incorporate the Examiner's suggestions made in the rejection under §112, second paragraph. Thus, it is respectfully requested that the Examiner withdraw the rejections of claims 1-6 and 14-15.

With respect to the rejection of claims 3-6, 14 and 15 as indefinite for the recitation of "alleles of BoLA-DRB3.2 are classified into the two or more groups of alleles," the Examiner has suggested that the claims be amended to clarify that the "two or more groups comprise 96 distinct BoLA-DRB3.2 alleles." However, Applicants note that the rejected claims recite the limitation "wherein the 96 kinds of alleles of BoLA-DRB3.2 are classified into" two or more groups, or 8 groups, depending on the claim. Applicants respectfully submit that this language already makes clear that the groups are comprised of the 96 alleles, and thus, any amendment would be unnecessary. Thus, it is respectfully requested that the Examiner withdraw the rejections of claims 3-6, 14 and 15.

With respect to the rejections of claims 14-15 for failure to recite a final process step, and for the use of the term "resulting sequences," Applicants respectfully submit that the current amendment to claim 14 renders these rejections moot, and makes clear that the "resulting sequence" is the sequence generated in (2). Applicants respectfully request that the Examiner withdraw the rejections of claims 14 and 15.

Response to §§ 102 Rejections

Claims 1-4, 7-10 and 14 are rejected under 35 U.S.C. § 102(b) as anticipated by Ellergren et al. The rejection asserts that Ellergren et al. teaches allele-specific primers which hybridize unique sequences in the BoLA-DRB3.2 gene. The rejection asserts that the primers taught by Ellergren et al. would be considered to be capable of amplifying alleles of one group and not of the remaining 7 groups.

With respect to the rejection of claims 7-10, Applicants have canceled claims 7-10 to pursue method claims at the present moment, and no estoppel should be inferred from Applicants action.

In response to the rejection of claims 1-6 and 14-15, Applicants note that Ellergren teaches the use of primers to identify polymorphisms of the DRB3-linked microsatellite locus in cattle by PCR of genomic DNA (page 270, column 1). Ellergren identifies a PCR amplification pattern of primers when used with the microsatellite alleles of exon 2 of the DRB3 gene. See page 273, Table 3. Ellergren does not teach, or suggest a method to amplify BoLA-DRB3.2 alleles using forward primers which amplify only one of two or more groups of alleles. Table 3 of Ellergren, which reveals the PCR amplification pattern of three alleles, shows that each of Elleregren's primers

amplified at least two different DRB3 alleles, as noted by the "+" in the columns. Thus, Ellergren does not teach the Applicants invention as recited in amended claim 1. Further, Ellergren does not teach the typing of BoLA-DRB3.2 alleles using PCR as recited in amended claim 14.

Therefore, Applicants respectfully request the Examiner withdraw the rejection of claims 1-6, and 14-15.

Claims 7-9 are rejected under §102(b) as being anticipated by Sitte et al.

In response, as discussed above, claims 7-9 have been canceled without prejudice, whereby this ground of rejection has been rendered moot.

Claims 1-4 and 6-10 are rejected under 35 U.S.C. § 102() [the Office Action did not specify which section of 102 was used as the basis for the rejection] as being anticipated by Aida. The rejection asserts that Aida teaches a primer B which is capable of amplifying all alleles of BoLA-DRB3.2 and a primer A which amplifies only DRB3.2 alleles that are fully complementary and is incapable of amplifying DRB3.2 alleles that are not fully complementary.

In response, Applicants note that Aida does not teach a method of amplifying BoLA-DRB3.2 for typing the different alleles, but instead is directed to identifying the susceptibility of the onset of bovine leukemia caused by the bovine leukemia virus BLV. See Column 2, lines 41-48. Aida teaches using a primer from among 8 primers to amplify bovine DNA encoding amino acids 75-78 of the β0 1 domain of the bovine MHC Class II DRβ chain. Column 2, lines 44-56. The various primers do not assist one of skill in the art in typing polymorphisms of the BoLA-DRB3.2 gene, they merely assist in identifying the sequence of amino acids 75-78.

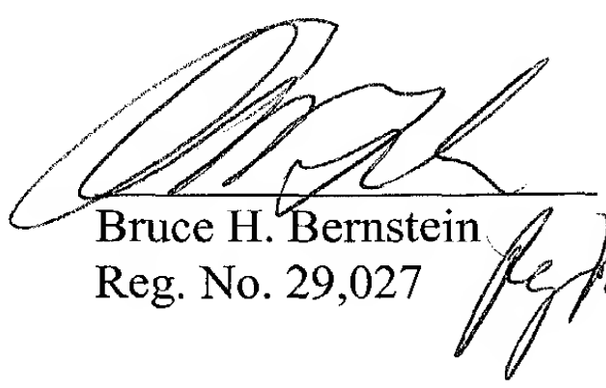
Thus, Aida does not teach, or suggest the current invention as recited in amended claim 1. Applicants, therefore, respectfully request that the Examiner withdraw the rejection of claims 1-4 and 6. As noted above, claims 7-10 have been canceled without prejudice.

CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Should the Examiner have any further comments or questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
Y. AIDA et al.



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